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TRANSMITTAL FORM

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March 28, 2000
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Kathy Dixon

Box Patent Application
Assistant Commissioner
For Patents
Washington, D.C. 20231

Attorney Doc. #: 64,600-024 CIP
Mailing Date: March 28, 2000

Dear Sir:

Transmitted herewith for filing is the patent application of:

Inventor(s): Yuh-Jiuan Lin and Yuh-Fan Liu

For: Method For Fabricating An Olfactory Receptor-Based Biosensor

This is a request for filing a:

___ Continuation _____ Divisional __X__ Continuation-in-Part (CIP)

prior application serial no. 09/ 057,181 filed on 04/08/98

Examiner: D. Fitzgerald Group/Art Unit: 1646

Submitted herewith are:

__X__ __5__ sheet of informal drawings showing Figs 1-5

_____ An Assignment of the invention to _____, together with Assignment Recordal Sheet

__X__ A Declaration for patent application under CFR 1.63 and 1.68

_____ A Preliminary Amendment

Mailing Date: March 28, 2000
Attorney Docket No.: 64,600-024 CIP

The filing fee has been calculated as shown below:

	No. Filed	No. Extra	Small Entity Fee	Large Entity Fee	Total
Basic Fee			$345.00	$690.00	$690.00
Total Claims	1 x20	x	$9.00	$18.00	
Indep. Claims	1 -3	x	$39.00	$78.00	
Multiple Dep. Clms.			$130.00	$260.00	$0
Assign. Rec. Fee			$40.00	$40.00	$0
TOTAL					$690.00

Maintenance of Copendency of Prior Application:

(This item must be completed and the papers filed in the prior application if the period set in the prior application has run)

X A petition, fee and response has been filed to extend the term in the pending prior application until March 30, 2000.

X A copy of the petition for extension of time in the prior application is attached.

____ Please charge my Deposit Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

X A check in the amount of $ 690.00 to cover the above calculated filing fee is enclosed

X The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0484. A duplicate copy of this sheet is enclosed.

X Any additional filing fees required under 37 CFR 1.6
X Any patent application processing fees under 37 CFR 1.17

Respectfully submitted,

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Enclosures

METHOD FOR FABRICATING AN OLFACTORY RECEPTOR-BASED BIOSENSOR

This application is a continuation-in-part of application 09/057,181 filed April 8, 1998, the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to biosensors and, more specifically, to biosensors which have biomolecules attached to a thin film transducer.

BACKGROUND OF THE INVENTION

Chemoreception is an ancient sense system that enables organisms to detect chemicals in its environment. In humans, odor receptor cells are located in the nose. The biochemical receptors for the odorants are transmembrane proteins found in the membrane of receptor cell cilia. Olfactory receptor proteins (ORP) generally have seven non-intersecting helices. It is believed that conserved residues determine the orientation of each helix relative to the other helices. When the odor molecule binds to the receptor (in the transmembrane regions), it is believed that the receptor molecule changes shape. This apparently activates a G-protein on the intracellular surface of the cilia which in turn binds to a G-protein receptor on the ORP. (Olfactory G-protein receptors are one of the largest groups of G-protein coupled receptors described to date.) Olfactory G-protein linked receptors then trigger the biochemical synthesis of neurotransmitters which open cation channels that ultimately lead to action potentials and signaling, i.e. the sense of smell. In other words, the chemical stimulus is transduced into a neural event. The major path of olfactory transduction is shown in Figure 1 of the drawings.

There is currently a need for sensors which can detect ligands of the type which bind to olfactory receptor proteins. The goal, then, is to assign functional odorants to specific olfactory receptors and to develop useful sensors for detecting the presence of the odorants. It has been difficult in the past, however, to rapidly determine the secondary and tertiary molecular structures of ORP's having olfactory receptor binding domains specific

to selected ligands of interest. This is due in part to the complexity of ORP molecules. As will be understood by those skilled in the art, in an empirical analysis, a determination of putative binding domains is an extremely labor-intensive endeavor. It begins with identification and molecular cloning of genes that code for the receptor protein of interest. These genes are then expressed and the target protein is isolated and purified. Physical studies such as X-ray diffraction, neutron diffraction and electron microscopy are conducted to determine 2-D maps and 3-D structure; site directed mutagenesis is conducted to determine the position of residues for ligand binding. It would be desirable to provide a method which eliminates as many of these steps as possible.

Thus, it is an object of the present invention to provide a method for rapidly determining ORP candidates for use as receptors for preselected odorant molecules.

It is a further object of the present invention to provide a method for fabricating a biosensor which includes a layer of polypeptides that selectively binds a preselected odorant molecule.

SUMMARY OF THE INVENTION

In one aspect the present invention provides a method for making a biosensor capable of detecting a molecule, wherein the molecule is a ligand for an olfactory receptor protein. The method includes the steps of determining the amino acid sequence of a preselected olfactory receptor protein the secondary and tertiary structures of which are not known. Typically this step will be carried out by choosing an ORP from a database of ORP's which have been sequenced. In the next step the amino acid sequence of the ORP selected in the first step is compared to the sequence of G-coupled protein receptors having known secondary and tertiary structures. This step will typically be carried out by accessing a database of G-protein receptors having known primary, secondary and tertiary structures. Next, based on primary sequence homology, one or more G-coupled protein receptors is chosen as a candidate on which to predict the secondary and tertiary structures of the unknown ORP. In the next step, the secondary and tertiary structures of the unknown ORP are approximated based on the known structures of the G-protein receptor

selected through sequence homology comparison in the prior steps. The approximated secondary and tertiary structures of the unknown ORP are then analyzed using conventional modeling techniques to identify likely binding domains for the ligand of interest. A polypeptide is then synthesized having the primary sequence of the most likely binding domain for the ligand. These polypeptides are attached to a transducer. The resultant biosensor is then tested by exposing it to the target ligand and determining binding efficiencies. By identifying and testing a number of polypeptides in this manner, high affinity biosensors can be rapidly fabricated.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a diagram illustrating the major pathway of olfactory transduction.

Figure 2 is a flow chart illustrating the modeling steps of the present invention.

Figure 3 is a perspective view of a transducer made in accordance with the present invention.

Figure 4 is an amino acid sequence for ORP P30955.

Figure 5 is a table illustrating frequency changes resulting from attachment of ligands to a polypeptide made in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to Figure 2 of the drawings, an olfactory receptor protein which has been sequenced is selected. Of course, it may be desirable in some cases to actually clone, express, isolate and sequence a new ORP; however, in most instances an ORP will be chosen from a sequence database having the primary amino acid sequence of various ORPs. One preferred database for use in the present invention is available on the ExPASy server of the Swiss Institute of Bioinformatics. Other similar databases or print sources may be equally suitable.

Once the ExPASy server has been accessed, the file entitled "SWISS PROT and TrEMBL- protein sequences" is opened. The ExPASy server is open to the public and may be accessed via the Internet. Next, using the keyword search feature of this file, the key words "olfactory receptor" may be used to create a subset of sequences of olfactory receptor proteins. An ORP is then selected, the sequence of which is to be used in the practice of the invention. The known sequence is displayed along with additional information on the ORP such as EMBL cross references, length and molecular weight. The amino acid sequence information is generally subdivided into potential extracellular and cytoplasmic domains.

In the next step of the invention the sequence of the ORP of unknown secondary and tertiary structures is compared to sequences of proteins having known sequences and known secondary structures. Most preferably, the database of proteins with known secondary structures is comprised of G-coupled receptor proteins. It will be appreciated by those skilled in the art that olfactory receptor proteins are a class of G-coupled receptor proteins. This comparison is preferably carried out using a publicly available database. Most preferably, the predicted secondary structure of the ORP under investigation is determined using the "PredictProtein" server of the "BIOcomputing 3D Modeling Unit Service" webpage (PredictProtein:B Rost (1996) Methods in Enzymology, 266:525-539; Url: http://dodo.cpmc.columbia.edu). The "PredictProtein" server includes: PHDsec (predicts secondary structure from multiple sequence alignments), PHDacc (predicts per residue solvent accessibility from multiple sequence alignments), PHDhtm (predicts the location and topology of transmembrane helices from multiple sequence alignments), GLOBE, TOPITS, MaxHom (dynamic multiple sequence alignment program which finds similar sequences in a database), EvalSec, COILS, ProSite (finds functional motifs in the sequence being investigated), SEG and ProDom (database of putative protein domains; searched with BLAST for domains corresponding to sequence being investigated) programs. In essence these servers allow the sequence of the ORP to be submitted for comparison to the sequences of proteins in the PredictProtein database. PredictProtein retrieves similar sequences and predicts secondary protein structure based on data for similar sequences. PredictProtein performs and displays the results of a "PROSITE" motif search, "ProDom" domain search, MAXHOM alignment header analysis, and provides information regarding

accuracy of the forgoing analyses. This prediction of secondary structure is performed by PredictProtein using a system of neural networks. The MAXHOM program produces a multiple sequence alignment file which serves as the input for the neural network system. The output of the MAXHOM analysis includes identification of aligned proteins, percentage of pairwise sequence identity, percentage of weighted similarity, number of residues aligned, number of insertions and deletions (indels), number of residues in all indels, length of aligned sequences and a short description of the aligned proteins. The preferred neural network for prediction of secondary structure is described in detail in: "Prediction of Protein Structure at Better than 70% accuracy" J. Mol. Biol., 1993, 232, 584-599, the entire disclosure of which is incorporated by reference. Prediction of solvent accessibility is also determined (PHDacc) in accordance with "The Analysis and Prediction of Solvent Accessibility in Protein Families" Proteins, 1994, 20, 216-226, the entire disclosure of which is incorporated by reference. The latter prediction provides values for the relative solvent accessibility. Prediction of helical transmembrane segments of the ORP is performed by the PHDhtm program. In this manner, the secondary structure (helix, sheet, loop) and location relative to the membrane (inside, outside, transmembrane) for the ORP under investigation is predicted with relative accuracy. Most preferably, the predicted topology for the transmembrane proteins is determined using PHDtopology and fold recognition is determined by predicted-based threading using PHDthreader. Again, the secondary structure predictive determinations are verified for accuracy using EvalSec. All of the computer programs used in the present invention can be accessed by the public and their disclosures are incorporated herein by reference. (see, embl-heidelberg.de/tmap_info.html).

Based on the results of the secondary structure prediction analysis, the sequences for the predicted seven transmembrane helices are determined. Next, the tertiary structure of the transmembrane helices are determined. Most preferably this is achieved in the present invention using the Swiss-Model 7TM Interface program and, preferably, BLAST (Basic local alignment search tool as described in J. Mol. Biol. 215:403-410, the entire disclosure of which is incorporated herein by reference). To begin, the complete sequence of the ORP under investigation is input in the BLAST program which then determines the most appropriate modeling template to be used in the tertiary structure investigation. The

modeling template will be that protein (of known primary, secondary and tertiary structures) having the highest primary sequence homology with the ORP to be investigated. In other words, using BLAST the primary sequence of the ORP under investigation is compared to the sequences of proteins in the 7TM subset of the SWISS-PROT database.

After the modeling template has been selected, the sequences of the helical regions are displayed and the sequences of the helices of the ORP under investigation (as determined in the secondary structure analysis step of the present invention) are input (Swiss-Model 7TM Interface program). That is, the helical regions of the template are aligned with the helical regions of the ORP under investigation. The comparison yields a prediction of the tertiary structure (3D in space) of the ORP being investigated on an atom-by-atom basis. The preferred protocol for this step takes into consideration energy minimization and the like as described in: "Promod and Swiss-Model: Internet-based Tools for Automated Comparative Protein Modeling, Biochem. Soc. Trans. V. 24 274 1996; Large-Scale Comparative Protein Modeling, Proteome Research: New Frontiers in Functional Genomics 177 1997; Swiss-Model and the Swiss-PDBviewer: an Environment for Comparative Protein Modeling, Electophoresis, V. 18 2714 1997; Automated Modeling of the Transmembrane Region of G-Protein Coupled Receptor by Swiss-Model, Receptors and Channels v. 4 161 1996; Protein Modeling by email, Bio/Technology V. 13 658 1995, the disclosures of which are incorporated by reference. (The preferred modeling software programs which can be used in the present invention have a high degree of sophistication. For example, ProMod is a knowledge-based approach to predictive structure determination. It requires at least one known 3D structure of a related protein and good quality sequence alignments; the degree of sequence identity affects the accuracy of the predictive structure. In ProMod, there is a superposition of related 3D structures. A multiple alignment with the sequence under investigation is made. A framework for the new sequence is made and any missing loops are rebuilt. The backbone of the structure is completed and corrected if required. Side chains are corrected and rebuilt. The resultant structure is verified and packing is checked. The structure is then refined by energy minimization and molecular dynamics considerations.)

The tertiary structures of the helices of the ORP under investigation are thus

determined and may be viewed stereoscopically using a program such as Insight II or Swiss PDB-viewer or the like. Next, a ligand, preferably one which is known to bind to the ORP under investigation, is selected. A number of assays may be used to determine high general binding affinities of various ligands for the ORP under investigation. The molecular structure of the ligand is then input to the Insight II program, i.e. the "tertiary or 3D structures of ORP helices and the ligand are input. Next, the most probably geometrical binding domains of the ORP under investigation and the ligand are determined, preferably using the Global Range Molecular Modeling program (GRAMM) which utilizes geometric recognition algorithms. As will be understood by those skilled in the art, GRAMM is a program for protein docking; no specific information about the binding sites is required. It performs a six-dimensional search through the relative translations and rotations of molecules. It takes an empirical approach to smoothing the intermolecular energy function by changing the range of atom-atom potentials. It allows the user to locate the area of the global minimum of intermolecular energy for structures of different accuracy. Insight II may then be used to calculate the energy distribution and reaction forces between the ligand and the geometrically predicted domains. The most probably overall binding domains are thus determined.

Polypeptides are then synthesized corresponding to these binding domains using conventional synthesis technologies. The polypeptides are then applied to the surface of a transducer, preferably one fabricated using thin film (semiconductor) techniques, as will be known to those skilled in the art. Briefly, with reference to Figure 3, biosensor 10 is seen having transducers 12 coated with polypeptide layer 14. Transducer 12 is preferably a piezoelectric quartz crystal-based device. A mass change will occur if a ligand binds to the polypeptide layer resulting any a measurable frequency change in the quartz crystal frequency, allowing detection of ligand binding. The success and efficience of the transducer can be determined, including by comparing the sensor's response to the ligand and other molecules.

Examples:

The following examples are intended to further illustrate the present invention.

A G-Protein Coupled Receptor database was accessed and the sequence of an ORP of known primary sequence, but unknown secondary and tertiary structures was retrieved (SWISS-PROT:P30955) as shown in Figure 4. It consists of 330 amino acids and has a molecular weight of 35197 daltons. The secondary structure was predicted and its accuracy verified through the use of MaxHom, PHDsec, PHDacc, PHDhtm, PHDtopology, PHDthreader and EvalSec. The transmembrane sequence regions were thus obtained.. A BLAST assisted template was then selected: Neuropeptide Y1 receptor (Homo sapiens). Trimethylamine was selected as the ligand. Using GRAMM, several possible binding domains were identified and corresponding polypeptides were generated. In Figure 5, (poly)peptide B1 designed in accordance with the present invention illustrates better response for trimethylamine than another (poly)peptide Pb2.

CLAIMS

What is claimed is:

1. A method of making a biosensor capable of detecting a molecule, wherein the molecule is a ligand for an olfactory receptor protein, said method comprising the steps of:

(a) Determining the amino acid sequence of a preselected olfactory receptor protein, the secondary and tertiary structures of said olfactory receptor protein being unknown;

(b) Comparing the amino acid sequence of said preselected olfactory receptor protein to known amino acid sequences of transmembrane proteins having known secondary and tertiary structures, said known amino acid sequences of said transmembrane proteins being selected from the group consisting of G-protein coupled receptors.

(c) Selecting at least one of said known amino acid sequences of said transmembrane proteins by determining which of said known amino acid sequences has the highest degree of sequence homology with the amino acid sequence of said preselected olfactory receptor protein;

(d) Using said selected sequence to approximate the secondary and tertiary structures of said preselected olfactory receptor protein;

(e) Using said approximated secondary and tertiary structures of said olfactory receptor protein to identify a likely binding domain of said olfactory receptor protein for said ligand;

(f) Synthesizing a polypeptide having the primary structure of said likely binding domain; and

(g) Attaching said synthesized polypeptide to the surface of a transducer.

ABSTRACT OF THE DISCLOSURE

A method for rapidly designing a biosensor which binds a preselected ligand to a layer of polypeptides. The polypeptide layer is made of relatively short molecules representative of a binding domain of an Olfactory Receptor Protein. The method uses a series of predictive structure determinations to obtain the sequence of the polypeptides applied to a transducer surface.

BH\248000.1
ID\ RLKdc

FIG 1

The major pathway of olfactory transduction

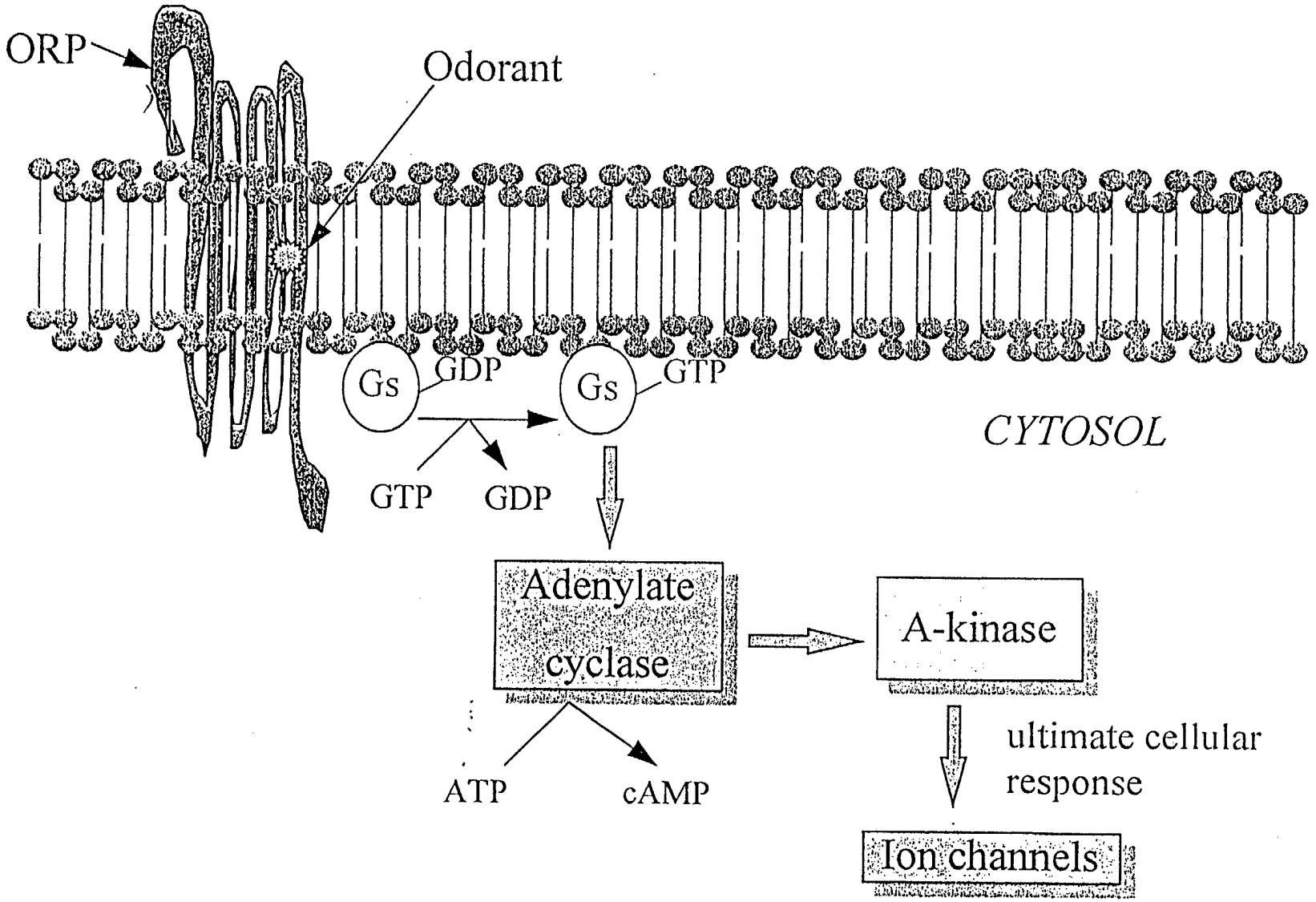
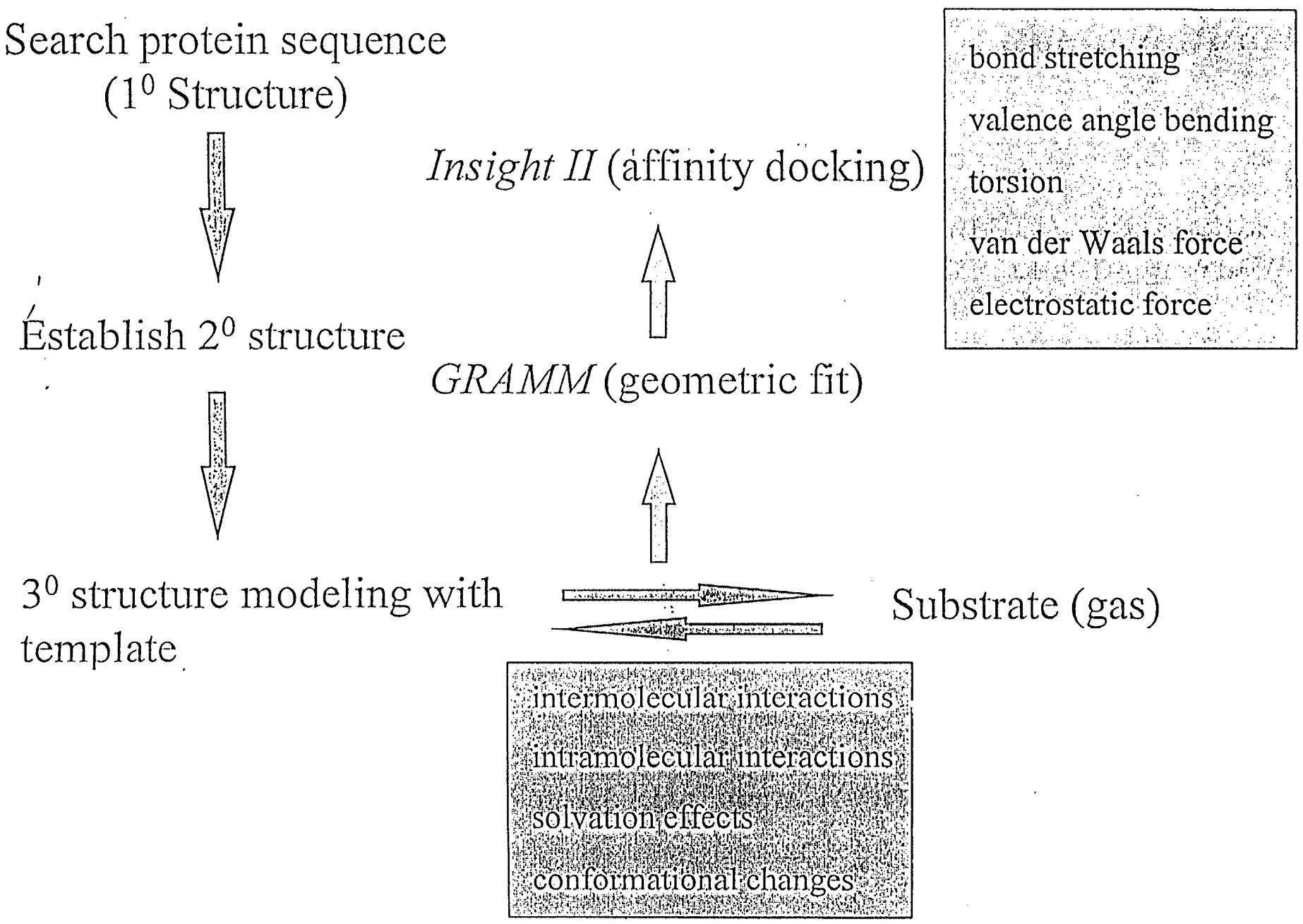


FIG 2


Search protein sequence
(1⁰ Structure)
Establish 2⁰ structure
3⁰ structure modeling with template
Insight II (affinity docking)
GRAMM (geometric fit)
Substrate (gas)
bond stretching
valence angle bending
torsion
van der Waals force
electrostatic force
intermolecular interactions
intramolecular interactions
solvation effects
conformational changes

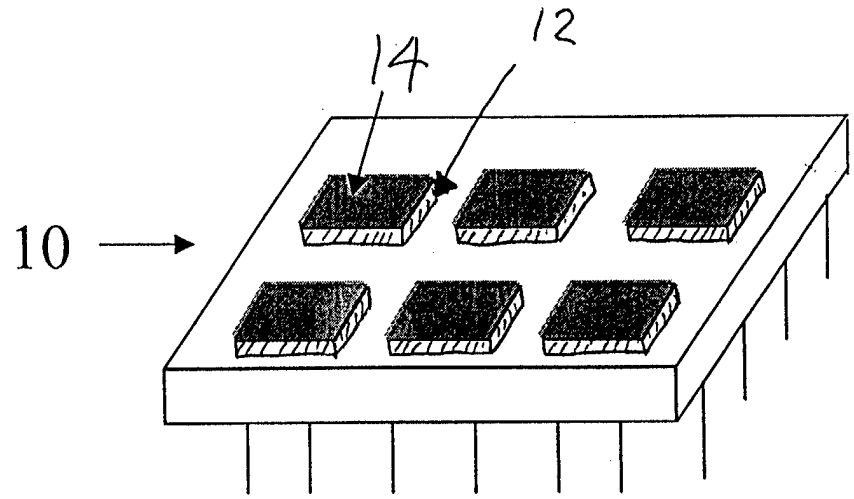


FIG 3

F 1624

Odorant/Olfactory Receptor Sequence of *Canis familiaris*:
(SWISS-PROT:P30955)

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MTEKNQTVVS EFVLLGLPID PDQRDLFYAL FLAMYVTTIL GNLLIIVLIQ LDSHLHTPM
LFLSNLSFSD LCFSSVTMPK LLQNMQSQVP SIPYAGCLTQ MYFFLFFGDL ESFLLVAMA
DRYVAICFPL HYTTIMSPKL CFSLLVLSWV LTMFHAVLHT LLMARLCFCA NTIPHFFCD
SALLKLACSD TQVNELVIFI MGGLILVIPF LLIITSYARI VSSILKVPSA IGICKVFST
GSHLSVVSLF YGTVIGLYLC PSANNSTVKE TIMAMMYTVV TPMLNPFIYS LRNKDMKGA
RRVICRKKIT FSV
```

Amino acids: 330
Molecular weight: 35197 dalton

SOURCE:
G protein Coupled Receptor DataBase (GPCRDB)
(*http://receptor.Mgh.Harvard.Edu/GCRDBHOME.Html*)

FIG 5

Gas of detected	Peptides	
	B1	Pb2
Trimethylamine (5.86ppm)	5696	221
Dimethylamine (3.78ppm)	3851	589
Ammonia (4.86ppm)	1022	345
Acetone (7.21ppm)	13	31
Formic acid (1.33ppm)	161	97
Ethanol (4.68ppm)	-5	16
Formaldehyde (6.54ppm)	-25	19

Peptide sequence of B1:DPDQRDC

Peptide sequence of Pb2: LFLSNLSFSDLCA

64,600-024CIP
ERSO 860068

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "METHOD FOR FABRICATING AN OLFACTORY RECEPTOR-BASED BIOSENSOR" the specification of which

__X__ is attached hereto.

_____ was filed on _____ as
Application Serial No. _____
And was amended on _____
(If applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendments referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56, a copy of which is attached.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application(s) for patent on inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			**Priority Claimed**	
Number	Country	Day/Month/Year	(Yes)	(No)
Number	Country	Day/Month/Year	(Yes)	(No)
Number	Country	Day/Month/Year	(Yes)	(No)

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I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

09/057,181	04/08/98	Pending
Application Ser. No.	Filing Date	Status
Application Ser. No.	Filing Date	Status

I further declare that I do not know and do not believe that the invention claimed in this application was ever known or used by others in this country before my invention thereof, or patented or described in any printed publication in any country before my invention thereof, or more than one year prior to this application or any prior U.S. application above identified in which said invention may have been disclosed, or in public use or on sale in the United States of America for more than one year prior to this application or any prior U.S. application above identified in which said invention may have been disclosed.

POWER OF ATTORNEY

And I hereby appoint as my attorneys with full power of substitution to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith to the firm of **Tung & Associates,** including the following individual attorneys associated with the firm:

Individual Attorney	**Reg. No.**
Randy W. Tung	31,311

Please send all correspondence concerning this application to the following address:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Full name of first joint inventor: YUH-JIUAN (First) LIN (Last)

Inventor's Signature _____

Date _____

Residence _____

_____

Citizenship Republic of China

Post Office Address _____

_____

Full name of second joint inventor YUH-FAN (First) LIU (Last)

Inventor's Signature _____

Date _____

Residence _____

Citizenship Republic of China

Post Office Address _____

_____

§1.56 Duty to disclose information material to patentability

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application; and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(I) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application;

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosection of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent or inventor.

(35 U.S.C. 6, Pub. L. 97-247)

[42 FR 5593. Jan. 28, 1977, as amended at 47 FR 21751, May 19, 1982; 48 FR 2710, Jan. 20, 1983; 49 FR 554, Jan. 4, 1984; 50 FR 5171, Feb. 6, 1985; 53 FR 47808, Nov. 28, 1988, effective Jan. 1, 1989; 57 FR 2034, January 17, 1992, effective March 6, 1992]